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Missed Opportunities to Prevent Mother-to-Child-Transmission in sub-Saharan Africa: Systematic Review and Meta-Analysis

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Abstract

Objectives—To determine magnitude and reasons of loss to programme and poor antiretroviral prophylaxis coverage in prevention of mother-to-child transmission (PMTCT) programmes in sub-Saharan Africa.

Design—Systematic review and meta-analysis.

Methods—We searched PubMed and Embase databases for PMTCT studies in sub-Saharan Africa published between January 2002 and March 2012. Outcomes were the percentage of pregnant women (i) tested for HIV, (ii) initiating antiretroviral prophylaxis, (iii) having a CD4 cell count measured, and (iv) initiating antiretroviral combination therapy (cART) if eligible. In children outcomes were (v) early infant diagnosis for HIV, and (vi) cART initiation. We combined data using random-effects meta-analysis and identified predictors of uptake of interventions.

Results—Forty-four studies from 15 countries including 75,172 HIV-infected pregnant women were analyzed. HIV-testing uptake at antenatal care services was 94% (95% confidence intervals [CI] 92–95%) for opt-out and 58% (95% CI 40–75%) for opt-in testing. Coverage with any antiretroviral prophylaxis was 70% (95% CI 64–76%) and 62% (95% CI 50–73%) of pregnant women eligible for cART received treatment. Sixty-four percent (95% CI 48–81%) of HIV exposed infants had early diagnosis performed and 55% (95% CI 36–74%) were tested between 12 and 18 months. Uptake of PMTCT interventions was improved if cART was provided at the antenatal clinic and if the male partner was involved.

Conclusions—In sub-Saharan Africa, uptake of PMTCT interventions and early infant diagnosis is unsatisfactory. An integrated family-centered approach seems to improve retention.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Contributions: Analyzed the data: CW, CM, OK. Wrote the paper: CW, GW, OK. Conceived and designed the systematic review: CW, ME, OK. Performed data extraction: CW, CM, NB, LS, JE, NB, GW, OK. Revised the paper: ME, MD.

Keywords

pre-ART; linkage to care; mortality; loss to follow-up; PMTCT; early infant diagnosis; prophylaxis

Introduction

In 2009 approximately 130,000 children were newly infected with HIV in sub-Saharan Africa, over 90% of them by vertical transmission [1, 2]. If HIV infected infants are left undiagnosed and untreated, about half of them die before the age of two [2]. Mother-to-child transmission, which occurs in 20 to 45% of HIV-infected pregnant women without antiretroviral prophylaxis, can be lowered to $\leq 5\%$ with adequate interventions [2]. Early infant diagnosis (EID) and treatment after delivery dramatically reduce infant mortality [3]. However, loss to follow-up of mothers and their infants from prevention of mother-to-child transmission (PMTCT) programs limits the impact of these interventions.

PMTCT interventions can be seen as a series of consecutive steps (Figure 1). When pregnant women first present at an antenatal care unit, they are tested for HIV. If positive, they are counseled for PMTCT and provided with antiretroviral medication. They are also assessed for eligibility for lifelong antiretroviral combination therapy (cART) and if they are eligible, therapy is initiated. With the option B+ approach for PMTCT this last step is unnecessary as all pregnant women start cART [4]. EID of HIV by polymerase chain reaction (PCR) is performed on infants if their mothers return with them for postnatal follow-up, preferably at around six weeks after delivery. In infants who test negative at EID or if no EID is available, the final HIV status is determined after weaning. Finally, cART is initiated in HIV-infected infants.

At each step of the PMTCT cascade, pregnant women and their infants may be lost to follow-up and not benefit from important health-care interventions. The magnitude and reasons for program attrition in sub-Saharan Africa remain poorly understood. We performed a systematic review and meta-analysis to evaluate the uptake of HIV testing and antiretroviral treatment in pregnant women and their children.

Methods

Data sources

We searched Pubmed and Embase databases on March 5th 2012, limiting the search to publications in the English language and studies published since 2002 (i.e. when the scale-up of ART programs in sub-Saharan Africa began) [5]. We used free text words as well as Medical Subjects Headings (MeSH) in Pubmed and Emtree-terms in Embase. We combined the following search terms and their variations: HIV, prevention of mother-to-child-transmission, infection of newborn, pregnancy, prenatal care, postnatal care, antiretroviral agents, eligibility, referral process and loss to follow-up. We examined the references of all included studies. Further details on the search strategy are given in the webappendix.

Study selection

We included all studies on pregnant women (with either unknown or positive HIV status) and their HIV-exposed infants who attended PMTCT programs in sub-Saharan Africa. We selected studies that reported the number of participants who were given access to at least one of the following interventions: initiation of antiretroviral prophylaxis for HIV positive pregnant women; assessment and initiation of lifelong cART; or HIV testing in infants. We

excluded qualitative studies, randomized controlled trials, modeling studies, studies where uptake of interventions was assessed by interview, and cost-effectiveness studies. Abstracts were screened according to a list of inclusion and exclusion criteria. Two reviewers independently assessed the eligibility of articles. Discrepancies were resolved by consensus.

Data extraction

Data extraction was performed in duplicate by eight reviewers using a standardized extraction sheet. The following data were extracted: characteristics of programs (setting, location, country) and participants (age, gestational age at first antenatal care visit), eligibility criteria for cART initiation and the number of participants completing the following steps: (i) HIV-testing of pregnant women; (ii) initiation of antiretroviral prophylaxis for mothers; (iii) CD4 cell count testing; (iv) initiation of cART in eligible women; (v) HIV diagnosis of the exposed infants around 6 weeks by PCR and between 12 and 18 months by PCR or antibody test; and (vi) cART initiation in infected infants (Figure 1). Eligibility was defined according to the programme threshold in use at the time of the study. We also extracted predictors of successful uptake of each step and recorded positive or negative associations with the outcomes studied. Discrepancies were resolved by consensus.

Statistical analysis

We assessed the percentage of participants who completed each of the steps, and estimated the underlying mean percentage by combining studies in random-effect meta-analysis. Calculations were done on the logit scale with results back-transformed to percentages. Results were heterogeneous with I^2 values consistently above 90% and p values from tests of heterogeneity <0.001 . We therefore calculated approximate prediction intervals (PrI) based on the whole random-effects distribution as well as traditional 95% confidence intervals (CI) around the mean of the distribution. PrI predict the likely underlying mean percentages in new studies and are the most sensible way to summarize the results of heterogeneous studies [6]. The percentage of women tested for HIV in programs with opt-in and opt-out strategies were compared in a random-effects meta-regression model. To calculate overall PMTCT-coverage, all regimens (single dose nevirapine at birth, dual and triple antiretroviral prophylaxis, as well as cART prescribed for life) were considered. For the meta-analysis on testing between 12 and 18 months postpartum, only infants from programs without PCR-testing or with negative early PCR test result were included. Data were analyzed using STATA version 12 (StataCorp, Texas, USA).

Results

Study and patient characteristics

We identified 146 potentially eligible full text articles out of 2,370 identified studies based on titles and abstracts. Fifty-six publications met our inclusion criteria but a further 12 articles were excluded because they reported on the same populations and time periods as other articles. A total of 44 studies including 75,172 HIV positive women were included. Details on the selection process are provided in the webappendix (Figure S1). The studies originated from 15 countries in sub-Saharan Africa (webappendix Figure S2). The number of patients in each publication ranged from 22 to 14,815 (Table 1) [7, 8]. Eight studies reported on the gestational age at presentation to antenatal care [9-16] the majority of women were in the late second or third trimester (webappendix Table S1). Many studies provided information on HIV testing (N=27) or antiretroviral prophylaxis without cART-eligibility assessment (N=23). Eligibility for cART was assessed in 14 programs, and 12 studies reported on cART-initiation in eligible women. Thirteen studies reported on uptake

of EID, eight on HIV testing between 12 and 18 months postpartum and one study reported on treatment initiation in infected infants (Figure 1).

HIV testing of pregnant women

In sites where provider initiated (opt-out) testing was performed, the combined estimate of women tested for HIV, based on nine studies, was 93.7%, with 95% CI of 92.4-95.0% and only slightly wider PrI of 88.7-98.6%. The combined estimate for opt-in testing, based on seven studies, was 57.6%, with a 95% CI of 40.0-75.1% and a PrI of 0-100% (Figure 2). The results from the two testing strategies were clearly different ($p < 0.001$ from meta-regression). Predictors of successful HIV testing were reported in six publications [10, 17-21] and included cART provision at the antenatal clinic [21] and being accompanied by a male partner [20] (webappendix Table S2).

Antiretroviral prophylaxis for PMTCT

The combined estimate of the percentage of HIV positive women receiving any type of prophylaxis, based on 34 studies, was 70.3%, with 95% CI and PrI of 64.3-76.3% and 33.7%-100.0%, respectively (Figure 3, webappendix Figure S3). In 19 of these programs, the only PMTCT intervention consisted of sdNVP at birth. In three studies, women initiated lifelong cART if eligible and received sdNVP otherwise. Dual or triple ART prophylaxis was available in nine studies, with an estimate of mean coverage of 58.6% and 95% CI and PrI of 41.0-76.2% and 0-100%, respectively (Figure 3, webappendix Figure S4). In six of these nine studies, some women received sdNVP even though dual or triple ART was available. The reason for this was that the women received sdNVP at their first visit but never returned for an assessment of ART eligibility [15, 22]. In three of the 34 studies the antiretroviral regimen was not specified. Information on predictors of sdNVP uptake was available in six studies [10, 13, 17, 19, 20, 23]. Uptake was better when the male partner was involved [20] and when women delivered at the health care facility [19] (webappendix Table S2).

Eligibility assessment and cART initiation

Ten studies reported on uptake of assessments of cART eligibility based on CD4 cell counts and subsequent cART initiation. In these studies, a CD4 cell count was determined in 67.6% of HIV-infected pregnant women (95% CI 37.5-97.8%; PrI 0- 100%). An estimated 22.3% of women who had a CD4 count were eligible for cART (95% CI 17.2-27.4%; PrI 3.0-41.6%) and an estimated 61.1% of these women initiated treatment (95% CI 47.7-74.5%; PrI 10.4-100%) (Figure 3, webappendix Figure S5). Results were similar when including all studies with information on any one of these steps (webappendix Figure S6): the estimated percentage of HIV positive women with a CD4 cell count, based on 14 studies, was 68.1% (95% CI 44.6-91.7%; PrI 0- 100%). Among these 22.6% of women were eligible for cART (95% CI 17.8-27.5%; PrI 3.9- 41.4%, based on 11 studies) and 61.5% of eligible women initiated cART (95% CI 49.8-73.2%; PrI 16.2-100, 11 studies,). Six studies assessed whether women with CD4 cell measurements returned to collect the results: an estimated 72.6% (95% CI 62.5-82.7%; PrI 35.5-100%) returned to the clinic.

Four studies reported on predictors for having a CD4 cell count recorded [8, 13, 18, 24]. A CD4 count was more likely to be recorded if the measurement was ordered on the same day as testing for HIV was done [8], if the result was available rapidly [8], if the test was done in urban areas [8], if the women was employed [18], or if the gestational age at the first visit was below 20 weeks [18]. Five studies reported on predictors for cART initiation in eligible women [8, 13, 18, 21, 24, 25]. Women were more likely to start cART if it was provided at the antenatal clinic [8, 24], if they were older [25], had more children [25], or presented earlier in pregnancy [21] (webappendix Table S2).

Linkage between PMTCT services, infant HIV diagnosis and cART initiation

The mean percentage of infants tested for HIV by PCR around 6 weeks based on 12 studies was 64.4% with 95% CI and PrI of 47.5-81.2% and 0%-100%, respectively (Figure 4, webappendix Table S3). Predictors for early infant diagnosis were reported in three studies [26-28]. These showed positive associations between uptake of testing and proximity to the clinic [26], large family size [26], early HIV diagnosis of the mother [27], or having received antiretroviral prophylaxis for PMTCT [27] (webappendix Table S2). The combined estimate of the percentage of infants tested between 12 and 18 months postpartum based on 7 studies was 55.2% with 95% CI 36.4-74.1% and PrI 0.0-100.0% (Figure 4, webappendix Table S3). Only one study followed the HIV infected children until cART initiation: 29.5% of infected infants could be traced to an ART clinic and of these about half initiated cART [29].

Discussion

Our meta-analysis included over 75,000 pregnant women from 15 countries in sub-Saharan Africa who had been enrolled in 44 studies of one or several steps of the PMTCT cascade. The results of the different studies were heterogeneous, and in some instances very heterogeneous, with maximally wide prediction intervals. Provider initiated (opt-out) HIV testing of pregnant women resulted in much higher coverage than patient-initiated (opt-in) testing, with an estimated 94% of women being tested with the first approach compared to 58% with the second. The uptake of antiretroviral prophylaxis for mothers was unsatisfactory, and the percentage of cART eligible patients who received the recommended treatment low. Overall, 70% of pregnant women received some form of antiretroviral prophylaxis, 64% of HIV exposed infants accessed early infant diagnosis by PCR around 6 weeks postpartum and 55% were tested between 12 and 18 months.

The risk of mother-to-child HIV transmission can be dramatically reduced by preventive measures including antiretroviral prophylaxis for the mother and the child [2]. According to a recent WHO update, the use of cART during pregnancy is preferable to mono- or dual therapy [4]. Our analysis showed that some women received sdNVP at their first visit and were then lost before dual or triple prophylaxis or cART could be initiated. In other cases it was unknown why the optimal regimen had not been provided even though it was available. Significantly, about one third of patients did not receive any type of antiretroviral prophylaxis, and 40% of cART eligible women did not initiate treatment. This finding is in line with recent systematic reviews on retention in HIV care, which reported that between 38% and 88% of pregnant women [30], and 32% and 37% of eligible patients from the general HIV infected population never started cART [31, 32]. An important difference between pregnant women and the general, HIV-infected population is that a substantially lower proportion of pregnant women were eligible for cART at first presentation (23% and 40% [31], respectively). This shows that with systematic HIV testing during pregnancy HIV infection can be diagnosed earlier, providing opportunities to initiate cART before patients present with advanced disease.

In a previous review Hensen *et al* [33] compared HIV-testing uptake before and after implementation of the opt-out strategy and found a substantial increase in uptake, from 10% to 66%. In our analysis, which included studies with either opt-in or opt-out testing, we found that the mean uptake was 94% with the opt-out strategy. The consistency of results across programs was striking and in contrast to the pronounced heterogeneity of results with the opt-in strategy. In general, pregnant women may be reluctant to be tested for many reasons, including structural and socio-cultural barriers [34, 35]. However, the provision of universal opt-out HIV-testing in antenatal care clinics might remove some of the fears related to patient-initiated testing, as it “normalizes” the testing process and integrates it into

routine clinical care. As a consequence, women might be less afraid of being stigmatized and judged by their peers. The studies included in this analysis showed enhanced uptake of testing if patients were accompanied by their male partner [20]. Finally, programmatic issues such as staff shortages or the unavailability of test kits might also limit HIV-testing uptake [36].

In our meta-analysis about two thirds of the HIV-exposed infants returned for EID and even less for HIV testing between 12 and 18 months postpartum. We analyzed coverage of HIV infant testing in programs where mothers were informed about the importance of testing their child. Preventing transmission from mothers who seroconvert while breastfeeding, or who are not attending an antenatal care clinic, is probably even more difficult than in women who attended an antenatal care clinic during pregnancy [37]. Several strategies aimed at increasing the uptake of infant testing have been evaluated [38]. For example, Rollins *et al* showed that universal HIV-testing of infants at immunization clinics was acceptable and feasible in rural South Africa, with 90% of women agreeing to have their infant tested [39]. WHO and most national guidelines recommend universal treatment of all HIV-infected children under two years of age. It is therefore important to develop effective strategies for testing children for HIV in infancy.

In order to increase the uptake of PMTCT interventions, our understanding of the individual and program-level factors that limit access to care must improve. Although few studies analyzed barriers to pre-ART care, integration of cART provision into routine antenatal services and reducing the number of visits seems promising. An example of this was the improved uptake of cART when the CD4 count was done on the same day as testing for HIV [8]. Better uptake was also associated with the provision of cART at the same place as PMTCT services [8, 21, 24], or if the distance to the clinic was short [8, 13]. In general, however, there is a lack of data on the effectiveness of integrating prevention of mother-to-child HIV transmission (PMTCT) programs with other health services. This is illustrated by a Cochrane review on this topic [40], which found only one study that matched the inclusion criteria. The involvement of the male partner may also increase the chance of successful interventions [20]. In a study from Côte d'Ivoire a family centered approach (i.e. provision of cART to partner and children; and improved access to contraception) helped to achieve coverage of over 90% from CD4 measurement to EID.

Our review provides a unique overview on the uptake of diagnostic and interventional steps throughout the PMTCT cascade in sub-Saharan Africa. The studies included in this review represent a wide range of urban, semi-urban and rural health care settings from many regions of sub-Saharan Africa. There are, however, several limitations: As noted previously, there were important differences between studies, which led to heterogeneous results and wide prediction intervals. Furthermore, the studies were conducted over eight years, a period in which HIV testing, treatment and prevention strategies evolved substantially. For example, the studies evaluating opt-out HIV-testing were performed later than those with opt-in strategies, possibly leading to bias due to an increase in the level of HIV awareness and quality of care over time. Most of the studies did not trace patients lost to follow-up or assess predictors for losses to program. They could thus not contribute to a better understanding of the reasons for attrition. In the context of initiation of lifelong cART in eligible women, we did not consider different CD4 cell count thresholds for starting cART, and studies did not report whether eligibility was based on CD4 cell count or stage of disease. Finally, none of the studies evaluated the option B+ approach and only one study reported on cART initiation in HIV-infected infants.

Conclusion

In order to reach the UNAIDS goal of eliminating paediatric HIV infections by 2015 [41], the coverage of PMTCT and cART need to be improved. Even though provider-initiated HIV-testing shows promising results, large gaps in antiretroviral prophylaxis, cART initiation, and infant testing remain. In order to improve retention in care of HIV-infected mothers and prevent new HIV-infections in children, a better understanding of the major barriers is of paramount importance. Further research on the major reasons for the failure of PMTCT programs in sub-Saharan Africa is urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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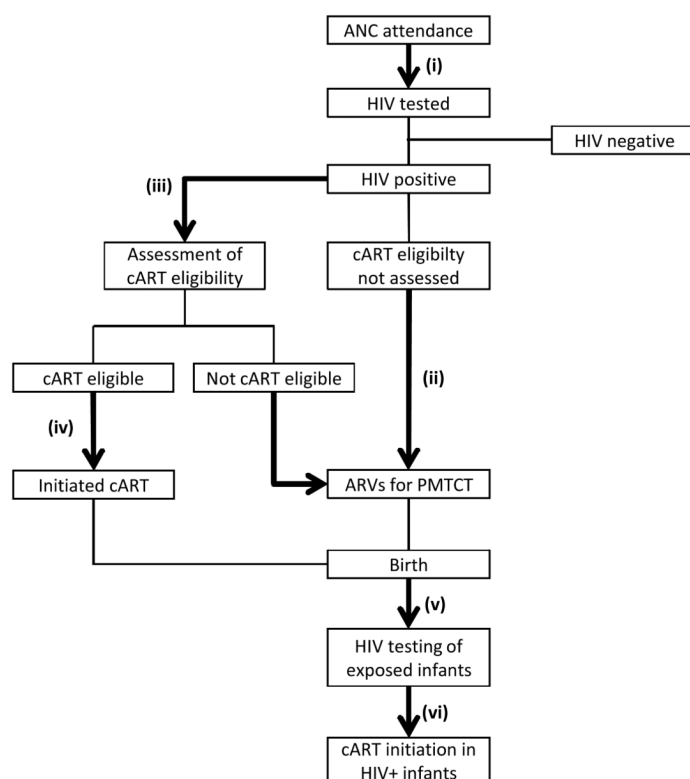
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Included studies reporting about the individual steps

- (i) HIV-testing**
27 studies
[7, 13-18, 20, 21, 23, 24, 28, 36, 42-55]
- (ii) ARV prophylaxis without prior cART eligibility assessment**
23 studies
[7, 9-12, 14, 16, 17, 20, 23, 27, 42, 45, 46, 48-51, 53-57]
- (iii) cART eligibility assessed**
14 studies
[8, 13, 18, 19, 21, 22, 24, 28, 36, 47, 52, 58-60]
- (iv) cART initiation**
12 studies
[8, 13, 18, 21, 22, 24, 25, 28, 44, 52, 58, 59]
- (v) HIV testing of exposed infants**
 - a) early infant diagnosis around 6 weeks:** 13 studies
[7, 11, 15, 19, 26-29, 36, 57, 59-61]
 - b) testing at 12-18 months postpartum:** 8 studies
[7, 9, 16, 43, 51, 54, 59, 61]
- (vi) Treatment initiation in HIV+ infants**
1 study
[29]

Figure 1. Steps of the prevention of mother-to-child-transmission cascade

Bold arrows represent steps with risk of attrition

ANC=antenatal care, cART=lifelong combination ART, ARVs=antiretroviral drugs, PCR=polymerase chain reaction

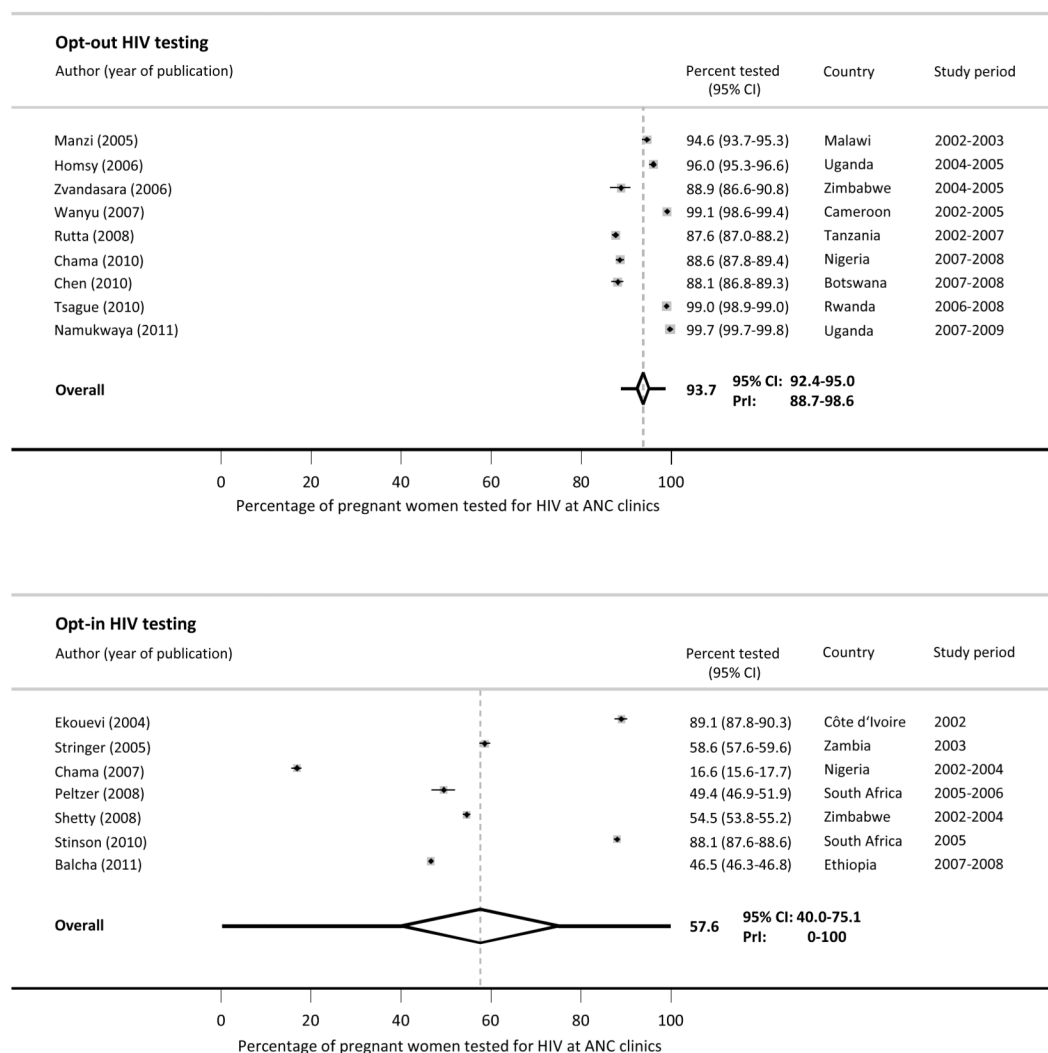


Figure 2. Meta-analyses of uptake of HIV testing in pregnant women by testing strategy

Top panel: Uptake of opt-out HIV testing

Bottom panel: Uptake of opt-in HIV testing

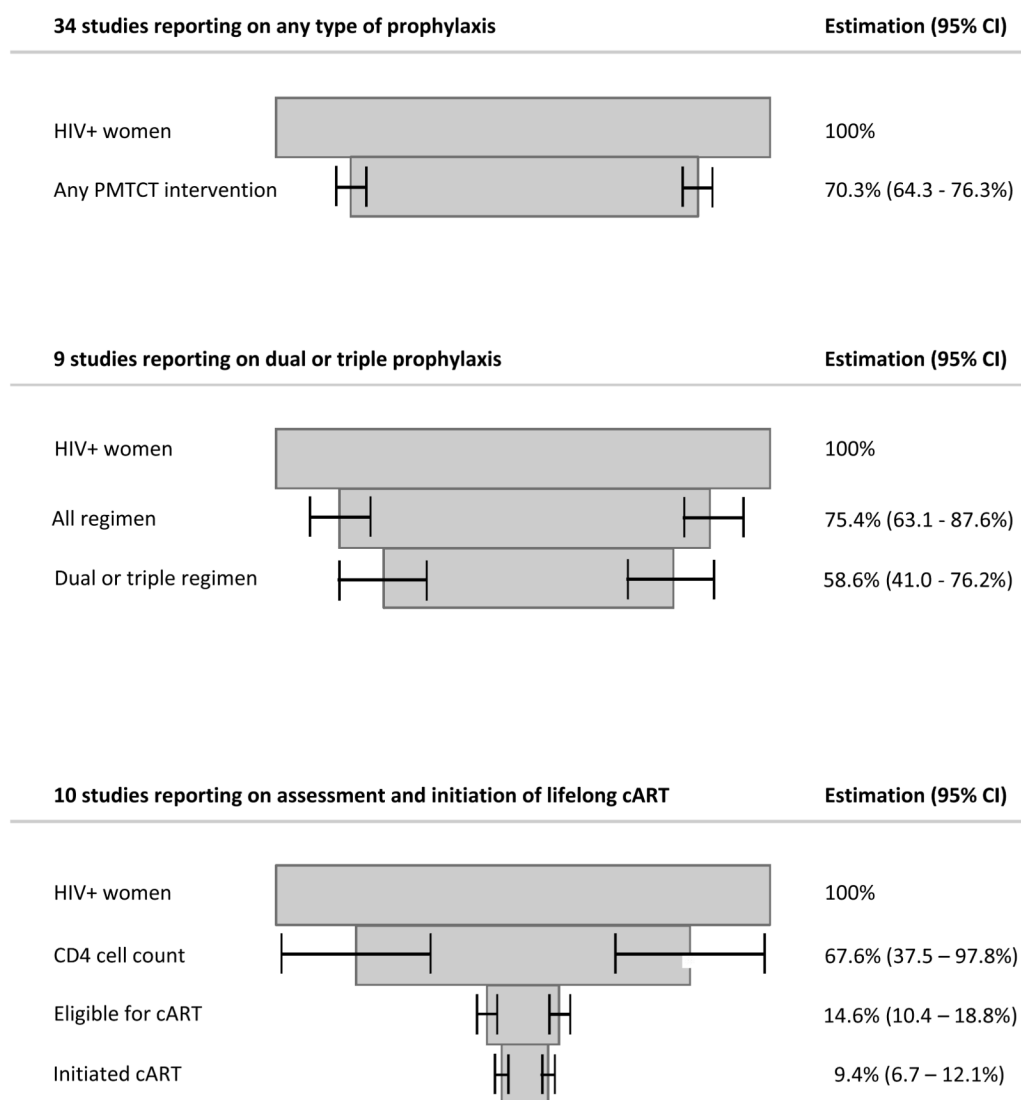
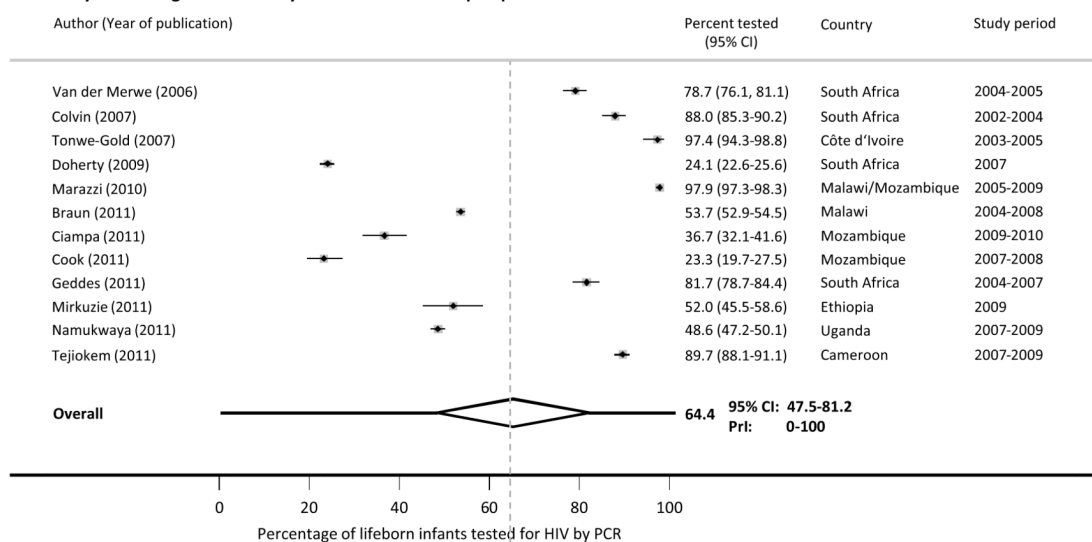


Figure 3. Coverage with antiretroviral drugs for prevention of mother-to-child-transmission (PMTCT)

Estimates are pooled estimates from meta-analyses providing data on the whole time period of each graph.

HIV+ = HIV positive, cART = antiretroviral combination therapy

Early infant diagnosis of HIV by PCR around 6 weeks postpartum



Infants tested for HIV between 12 and 18 months postpartum

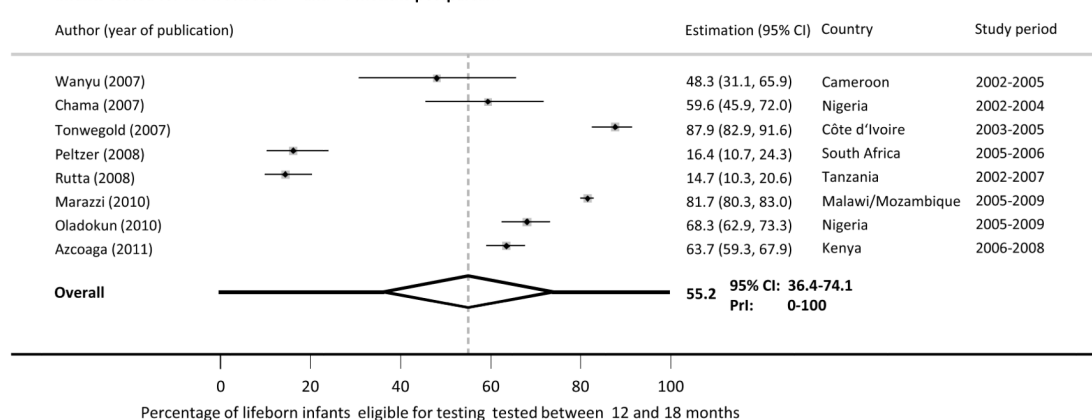


Figure 4.

Uptake of early infant diagnosis by polymerase chain reaction (PCR) around 6 weeks postpartum and infant testing between 12 and 18 months postpartum if the program did not provide early infant diagnosis by PCR or the child was HIV negative at PCR testing.

Table 1

Characteristics of included studies

Author (publication year)	Study-Period	No. HIV+ pregnant women incl in study	No. of HIV exposed newborns incl in study	Location (No. of sites, city or region, country)	Setting	Inclusion/exclusion criteria for participants	Eligibility for cART (cells/mm ³), WHO stage	PMCT regimen (Pregnant women/exposed infant)	Age at Infant testing
Azcoaga-Lorenzo (2011)	2006-2008	1668	485	11 sites, Busia District, Kenya	n.r.	All pregnant women attending ANC	n.r.	cART, AZT+3TC+sdNVP/sdNVP+AZT	6 weeks, 6 weeks after weaning 2 nd test
Balcha (2011)	2007-2008	2232	2232	112 sites, Oromia region, Ethiopia	n.r.	All pregnant women attending ANC	n.r.	sdNVP/sdNVP	n.r.
Barigye (2010)	2002-2007	109	106	9 sites, Kyamulibwa sub-county, Uganda	Rural	All HIV-tested pregnant women attending ANC	n.r.	cART, sdNVP/sdNVP	n.r.
Behets (2009)	2003-2005	792	395	21 sites, Kinshasa, Democratic Republic of Congo	Urban	All pregnant women attending ANC	n.r.	sdNVP/sdNVP	n.r.
Braun (2011)	2004-2008	14669	14669	6 sites, Lilongwe District, Malawi	Urban	All HIV-tested pregnant women attending ANC and infants born and tested since 2004	<250 III+IV	cART, sdNVP/sdNVP	6 weeks, 6 weeks after weaning
Chama (2007)	2002-2004	92	52	1 site, Maiduguri, Nigeria	Urban	All pregnant women attending ANC	<200 III+IV	cART, sdNVP/sdNVP	18 months
Chama (2010)	2007-2008	695	506	1 site, Maiduguri, Nigeria	Urban	All pregnant women attending ANC	<200 III+IV	cART, AZT+3TC+IND/r, TDF+FTC+IND/r /sdNVP+AZT	6 and 13 weeks, every 3 month, last test 3 month after weaning
Chandisarewa (2007)	2004-2005	1439	443	4 sites, Chitungwiza, Zimbabwe	Urban	All pregnant women attending ANC	n.r.	sdNVP/sdNVP	n.r.
Chen (2010)	2007-2008	793	n.r.	1 site, Gaborone, Botswana	Urban	All pregnant women attending ANC and delivering within study period, >20 weeks of gest age at delivery	<200/<250 IV	cART, AZT+sdNVP/n.r.	n.r.
Chi (2007)	2005	680	n.r.	1 site, Lusaka, Zambia	Urban	All newly HIV+ diagnosed pregnant women attending ANC	<200 IV	AZT+sdNVP, sdNVP/n.r.	n.r.

Author (publication year)	Study-Period	No. HIV+ pregnant women incl in study	No. of HIV exposed newborns incl in study	Location (No. of sites, city or region, country)	Setting	Inclusion/exclusion criteria for participants	Eligibility for cART CD4 count (cells/mm ³), WHO stage	PMCT regimen (Pregnant women/exposed infant)	Age at Infant testing
Ciampa (2011)	2009-2010	395	395	2 sites, Alto molôcué and Namacurra, Zambézia Province, Mozambique	Rural	All HIV+ pregnant women who gave birth at study hospital	<350 III+IV	cART, AZT+3TC/ sdNVP, AZT	4 weeks
Colvin (2007)	2002-2004	665	665	3 sites, Paarl, Rietvlei, Umlazi, South Africa	Rural, semi-urban	All HIV+ pregnant women and their infants attending ANC at 3 of the 18 national PMTCT pilot sites	n.r.	sdNVP/sdNVP	3-4 weeks
Cook (2011)	2007-2008	450	450	1 site, Alto molôcué, Mozambique	Rural	All HIV+ pregnant women attending ANC, mother infant pairs were excluded if infant was ineligible for DBS PCR at postnatal follow-up (<1mth or >18mth)	n.r.	cART, AZT+sdNVP, sdNVP/sdNVP+AZT, sdNVP	1-18 months
Creek (2007)	2003-2004	345	n.r.	4 sites, Francistown, Botswana	Urban	All pregnant women attending ANC	n.r.	AZT/n.r.	n.r.
Doherty (2009)	2007	3071	3071	21 sites, Abajuba District, South Africa	n.r.	All pregnant women attending ANC	n.r.	sdNVP / sdNVP	6 weeks
Ekouevi (2004)	2002	226	n.r.	5 sites, Abidjan, Côte d'Ivoire	Urban	All pregnant women attending ANC	n.r.	AZT+sdNVP/n.r.	n.r.
Geddes (2011)	2004-2007	703	699	1 site, Durban, South Africa	Urban	All pregnant women attending ANC	<200	cART, AZT+sdNVP, triple-ARV*/sdNVP+AZT, sdNVP	6 weeks
Homsy (2006)	2004-2005	278	n.r.	1 site, Tororo, Uganda	Rural	All pregnant women attending ANC	n.r.	sdNVP/sdNVP	n.r.
Kasenga (2009)	2005-2007	635	n.r.	1 site, Makwasa, Malawi	Rural	All pregnant women attending ANC	n.r.	sdNVP/sdNVP	n.r.
Kiptoo (2009)	2005-2006	309	n.r.	3 sites, Kitale, Kapsabet, Nandi Hills, Kenya	Rural	All pregnant women attending ANC for the 1 st time during current pregnancy	<200	ARV*/n.r.	n.r.
Kirere (2008)	2002-2004	94	101	1 site, Oicha, Democratic Republic of Congo	Rural	All pregnant women attending ANC with gest age > 36weeks	n.r.	sdNVP/sdNVP	n.r.
Kouam (2006)	2003-2004	22	18	1 site, Yaoundé, Cameroon	Urban	All pregnant women attending ANC	n.r.	sdNVP/sdNVP	6 weeks, 6 and 15-18

Author (publication year)	Study-Period	No. HIV+ pregnant women incl in study	No. of HIV exposed newborns incl in study	Location (No. of sites, city or region, country)	Setting	Inclusion/exclusion criteria for participants	Eligibility for cART CD4 count (cells/mm ³), WHO stage	PMCT regimen (Pregnant women/exposed infant)	Age at Infant testing
Kunwenda (2011)	2004-2009	3335	n.r.	6 sites, Blantyre, Malawi	Urban	All HIV+ pregnant women attending ANC or giving birth at study site, willing to return for postnatal follow-up and breastfeed the infant	<250	cART, sdNVP/sdNVP+AZT	n.r.
Mandala (2009)	2007-2008	14815	n.r.	60 sites, Northern, Luapula, Copperbelt, Central, North Western Province, Zambia	Rural	All HIV+ pregnant women attending ANC	<350 IV	cART, ARV*, sdNVP/ARV*	n.r.
Manzi (2005)	2002-2003	646	206	69 sites, Thylo District, Malawi	Rural	All pregnant women attending ANC	n.r.	sdNVP/sdNVP	18 months
Marazzi (2010)	2005-2009	3273	3148	19 DREAM centers and 4 laboratories, Malawi and Mozambique	n.r.	All HIV+ pregnant women attending ANC, availability on data on pregnancy outcome, intent to follow-up in program, willing to breastfeed	<350	cART, triple ARV*/n.r.	4 weeks, 6 and 12 months
Mirkuzie (2011)	2009	282	221	15 sites, Addis Ababa, Ethiopia	Urban	All HIV+ pregnant women attending ANC and infant ≥6 weeks of age at closure of study	<200	cART, AZT+3TC+sdNVP /sdNVP+AZT	6 weeks
Moodley (2011)	2007	258	n.r.	2 sites, Umlazi catchment area, Kwa-Zulu-Natal, South Africa	Semi-urban, urban	All women presenting at postnatal ward within 48h of delivery	<200	cART, sdNVP/sdNVP	n.r.
Msuya (2006)	2002-2004	184	n.r.	2 sites, Majengo and Pasua, Tanzania	Urban	All pregnant women attending ANC, were pregnant in 3 rd trimester, resident of Moshi urban district	n.r.	sdNVP/sdNVP	n.r.
Namukwaya (2011)	2007-2009	7941	4807	1 site, Kampala, Uganda	Urban	All HIV+ pregnant women attending ANC	<250/<350 III+IV	cART, AZT+3TC+sdNVP, AZT+sdNVP/sdNVP+AZT	6 weeks

Author (publication year)	Study-Period	No. HIV+ pregnant women incl in study	No. of HIV exposed newborns incl in study	Location (No. of sites, city or region, country)	Setting	Inclusion/exclusion criteria for participants	Eligibility for cART (CD4 count (cells/mm ³), WHO stage)	PMCT regimen (Pregnant women/exposed infant)	Age at Infant testing
Oladokun (2010)	2002-2007	2157	303	1 site, Ibanan, Nigeria	Urban	All pregnant women attending at ANC, babies born until end of 2005	n.r.	ARV*/n.r.	18 months
Orie (2009)	2007	227	227	1 site, Pietermaritzburg, South Africa	Urban	All pregnant women attending ANC and delivering at regional hospital, women who did not attend ANC at hospital were excluded	<200 IV	cART, sdNVP/sdNVP	n.r.
Peltzer (2008)	2005-2006	116	116	5 sites, Quakeni Area, South Africa	Rural	All pregnant women with confirmed HIV status, women with unknown HIV status were excluded	n.r.	sdNVP/sdNVP	9 months
Rutia (2008)	2002-2007	301	184	6 sites, Greater Lukole camp, Nagara District, Tanzania	Rural	All pregnant women attending ANC	n.r.	sdNVP/sdNVP	18 months
Shetty (2008)	2002-2004	1986	727	4 sites, Chitungwiza, Zimbabwe	Semi-urban	All pregnant women attending ANC	n.r.	sdNVP/sdNVP	n.r.
Stinson (2010)	2005	3498	380	4 sites, Cape Town, South Africa	Urban	All pregnant women attending ANC	<200	cART, AZT+sdNVP, sdNVP/sdNVP	n.r.
Stringer (2005)	2003	1140	1140	25 sites, Lusaka, Zambia	Urban	All pregnant women attending ANC, mother with delivery before arrival at clinic were excluded	n.r.	sdNVP/sdNVP	n.r.
Teijokem (2011)	2007-2009	1587	1587	3 sites, Douala and Yaounde, Cameroon	Urban	All life-born infants to HIV+ mothers who enrolled in the 1 st phase of the PEDICAM study, random exclusion of 1 of the infants in cases of twins	n.r.	ARV*/n.r.	6 weeks
Towne-Gold (2007)	2003-2005	261	231	2 sites, Abidjan, Cote d'Ivoire	Urban	All pregnant women enrolled in the MTCT plus Initiative,	<200 IV	cART, AZT+3TC+sdNVP, sdNVP/sdNVP+AZT	4 weeks, 12 months

Author (publication year)	Study-Period	No. HIV+ pregnant women incl in study	No. of HIV exposed newborns incl in study	Location (No. of sites, city or region, country)	Setting	Inclusion/exclusion criteria for participants	Eligibility for cART (CD4 count (cells/mm ³), WHO stage)	PMCT regimen (Pregnant women/exposed infant)	Age at Infant testing
exclusion of PW with HIV-2 infection, exclusion of 2 nd rank child in cases of twins/multiple birth									
Tsague (2010)	2006-2008	2048	n.r.	32 sites, Kibuye Region, Gisenyi Region and Kigali, Rwanda	n.r.	All pregnant women attending ANC	<350 IV	cART, scAZT+3TC+sdNVP/sdNVP+AZT	n.r.
Tukur (2007)	2003-2005	125	n.r.	1 site, Kano, Nigeria	Urban	All HIV+ pregnant women delivering at study hospital	n.r.	cART, tripple-ARV, sdNVP/sdNVP	3 days
Van der Merwe (2006)	2004-2005	1027	1027	1 site, Johannesburg, South Africa	Urban	All HIV+ pregnant women attending ANC	<250 IV	cART, sdNVP/sdNVP	6 weeks
Wanyu (2007)	2002-2005	82	64	20 sites, Cameroon	Rural	All pregnant women counseled by traditional birth attendant	n.r.	sdNVP/sdNVP	15 months
Zvandasara (2006)	2004-2005	340	335	1 site, Harare, Zimbabwe	Urban	All pregnant women referred to ANC	n.r.	sdNVP/sdNVP	n.r.

cART = lifelong antiretroviral therapy, sdNVP = single dose nevirapine at birth, AZT = zidovudine, 3TC = lamivudine, IND/r = ritonavir boosted indinavir, TDF = tenofovir, FTC = emtricitabine,

ANC = antenatal care. HIV+ = HIV positive, incl = included, n.r. = not reported, MTCT = mother-to-child-transmission

* ARV = antiretroviral prophylaxis, regimen not specified, triple-ARV = triple prophylaxis including different regimens